Supplemental Data

Highly Efficient and Selective Synthesis of Xerulin *via* Pd-Catalyzed Cross Coupling and Lactonization Featuring (*E*)-Iodobromoethylene as a Novel Two-Carbon Synthon

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(*E*)-1-Iodo-2-bromoethylene.[a] Acetylene[b] was slowly bubbled through a solution of iodine monobromide[c] (24 g, 116 mmol) in 48% HBr (150 mL) at 0 °C over 1 h; the solution was further stirred under acetylene atmosphere for 48 h. (The product precipitated as it was formed.) The reaction mixture was warmed to 20 °C and extracted with pentane. The pentane extracts were washed with brine (until neutral), aqueous $Na_2S_2O_3$, and brine. Removal of solvent followed by distillation afforded 19.8 g of the title compound (73% yield): bp 65 °C at 42 mm Hg (50 °C/25 mmHg); ^{1}H NMR ($CDCl_3$) δ 6.75 (d, J = 13.5 Hz, 1 H), 6.86 (d, J = 13.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 76.71, 109.99; IR (neat) 3020, 1615, 1560, 1139, 391, 711, 627 cm^{-1}; HRMS calculated for C_2H_2BrI: 231.8585; found: 231.8385.

(*E*)-4-Bromo-1-(*tert*-butyldimethylsilyl)-3-buten-1-yne. To a solution of (*tert*-butyldimethylsilyl)acetylene (1.86 mL, 10 mmol) in THF (10 mL) was added *via* a syringe MeMgBr (3.7 mL of 3 M ether solution; 11 mmol). The reaction mixture was stirred for 3 h at 25 °C, and a solution of anhydrous $ZnBr_2$ (2.9 g, 13 mmol) in THF (5 mL) was added at 0 °C. The mixture was stirred at 0 °C for 30 min and added *via* cannula to a solution of (*E*)-1-iodo-2-bromoethylene (2.56

g, 11 mmol) and $(Ph_3P)_4Pd$ (0.23 g, 0.02 equiv) in THF (5 mL). The resultant mixture was stirred at 25 °C for several hours, quenched with aqueous NH_4Cl, and extracted with ether. Ether fraction was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. Flash chromatography (silica gel, pentane) afforded 1.72 g (70% yield) of the title compound as a colorless liquid: bp 100 °C (20 mm Hg); ^1H NMR ($CDCl_3$) δ 0.13 (s, 6 H), 0.94 (s, 9 H), 6.22 (d, J = 14 Hz, 1 H), 6.75 (d, J = 14 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ -4.80 (2C), 16.56, 26.04 (3C), 95.77, 101.53, 117.71, 119.94; IR (neat) 2954, 2166, 2109, 1695, 1471, 1251, 1063, 811 cm^{-1}.

(*E*)-1-(*tert*-Butyldimethylsilyl)-3-hexen-1,5-diyne. Ethylnylmagnesium bromide (1.5 mmol, 3mL of 0.5 M THF solution) was added to a solution of anhydrous $ZnBr_2$ (450 mg, 2 mmol) in THF (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. To this were added 1-(*tert*-butyldimethylsilyl)-3-buten-1-yne (123 mg, 0.5 mmol) and then $(Ph_3P)_4$ Pd (29 mg, 5 mol %). The reaction mixture was stirred at 20 °C for 16 h, quenched with 3% HCl, and extracted with ether. The ether extract was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. Chromatographic purification (alumina, pentane) afforded 73 mg of the title product (77% yield): ^1H NMR ($CDCl_3$) δ 0.13 (s, 6 H), 0.94 (s, 9 H), 3.17 (d, J = 2.2 Hz, 1 H), 5.98 (dd, J = 16.1 and 2.2 Hz, 1 H), 6.09 (d, J = 16.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ-4.78 (2C), 16.63, 26.05 (3C), 81.66, 82.47, 99.33, 103.09, 120.69, 122.88; IR (neat) 3304, 2955, 2930, 2174, 2125, 1587, 1471, 1251, 1080, 825, 628 cm^{-1}; HRMS calculated for $C_{12}H_{18}Si$: 190.1178; found 190.1181.

(*E*)-5-Hepten-1,3-diyne: ^1H NMR ($CDCl_3$) δ 1.83 (dd, J = 6.9 and 1.8 Hz, 3 H), 2.36 (d, J = 1.0 Hz, 1 H), 5.51 (ddq, J = 15.8, 1.8, and 1.0 Hz, 1 H), 6.35 (dq, J = 15.8 and 6.9 Hz, 1 H).

(1*E*,7*E*)-1-Bromo-1,7-nonadien-3,5-diyne (2): ^1H NMR ($CDCl_3$) δ 1.82 (dd, J = 6.9 and 1.8 Hz, 3 H), 5.56 (ddq, J = 15.8, 1.8 and 1.0 Hz, 1 H), 6.27 (dd, J = 14.0 and 1.0 Hz, 1 H), 6.37 (dq, J = 15.8 and 6.9 Hz, 1 H), 6.8 (d, J = 14 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.22, 72.12, 76.56, 76.96,

82.27, 109.84, 116.94, 122.03, 144.70; IR (neat) 2928, 2361, 2202, 1550, 1438, 1197, 946, 913 cm^{-1}; HRMS calculated for C_9H_7Br, 193.9731: found, 193.9735.

(3*E*,5*E*,7*E*,13*E*)-1-(*tert*-Butyldimethylsilyl)-3,5,7,13-pentadecatetraen-1,9,11-triyne. A solution of (*E*)-1-(*tert*-butyldimethylsilyl)-3-hexen-1,5-diyne (177 mg, 0.93 mmol) in benzene (1 mL) was added to a suspension of Cp_2ZrClH (267 mg, 0.89 mmol, 95% activity) in benzene (2 mL). The reaction mixture was stirred for 1 h to give a transparent solution. GLC analysis of an aliquot indicated total consumption of the starting material. ^1H NMR analysis of an aliquot with mesitylene as an internal standard indicated the formation of the desired alkenylzirconium derivative in 80% yield. Benzene was removed *in vacuo* and THF (3 mL) was added. A catalyst prepared from $(Ph_3P)_2PdCl_2$ (11 mg, 5 mol %) and DIBAH (30 mL of 1 M hexane solution, 10 mol %) in THF (1 mL) was added, which was followed by (1*E*,7*E*)-1-bromo-1,7-nonadien-3,5-diyne (59 mg, 0.3 mmol, in 1 mL THF) and $ZnCl_2$ (27 mg, 0.2 mmol in 1 mL THF). The reaction mixture was stirred for 16 h at 25 °C, quenched with aqueous NH_4Cl, and extracted with pentane. The pentane extract was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. Chromatographic purification (silica gel, pentane) afforded 87 mg of the title product (95% yield, 97% purity): ^1H NMR ($CDCl_3$) δ 0.13 (s, 6 H), 0.95 (s, 9 H), 1.84 (dd, J = 6.9 and 1.9 Hz, 3 H), 5.61 (apparent d, J = 15.6 Hz, 1 H), 5.71 (d, J = 15.6 Hz, 1 H), 5.73 (d, J = 15.2 Hz, 1 H), 6.3-6.35 (m, 3 H), 6.6-6.65 (m, 1 H), 6.7-6.8 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ -4.43 (2C), 16.91, 19.20, 26.32 (3C), 72.77, 78.93, 80.75, 83.13, 98.62, 105.33, 110.16, 111.93, 113.84, 133.97, 135.10, 142.04, 143.93, 144.03; IR (neat) 2927, 2859, 2150, 2108, 1468, 1248, 993, 858 cm^{-1}; HRMS: calculated for $C_{21}H_{26}Si$: 306.1804, found 306.1808.

(3*E*,5*E*,7*E*,13*E*)-3,5,7,13-Pentadecatetraen-1,9,11-triyne. To a solution of (3*E*,5*E*,7*E*,13*E*)-1-(*tert*-butyldimethylsilyl)-3,5,7,13-pentadecatetraen-1,9,11-triyne (153 mg, 0.5

mmol) in THF (5 mL) was added at -78 °C tetrabutylammonium flouoride (0.53 mmol, 0.53 mL of 1 M THF solution). After stirring at -78 °C for 10 min and 0 °C for 5 min (TLC monitored, 95/5 hexane-EtOAc), the reaction mixture was quenched with water and extracted with ether, washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. Chromatographic purification (silica gel, 95/5 hexane-EtOAc) afforded 92 mg of the title product (96% yield) which was used immediately after purification: ^{1}H NMR ($CDCl_3$) δ 1.84 (dd, J = 6.9 and 2 Hz, 3 H), 3.17 (d, J = 2.4 Hz, 1 H), 5.61 (d, finely split, J = 15 Hz, 1 H), 5.67 (dd, J = 15.7 and 2.4 Hz, 1 H), 5.75 (d, J = 15.6 Hz, 1 H), 6.3-6.4 (m, 3 H), 6.65-6.75 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.21, 72.70, 79.01, 80.61, 81.98, 83.19, 83.24, 110.13, 112.31, 112.56, 134.37, 134.66, 142.79, 143.76, 144.12. No further characterization of this compound was performed.

Xerulin (1). A mixture of (3*E*,5*E*,7*E*,13*E*)-3,5,7,13-pentadecatetraen-1,9,13-triyne (80 mg, 0.41 mmol), (*Z*)-3-iodoprop-2-enoic acid (99 mg, 0.50 mmol), $Pd(PPh_3)_4$ (24 mg, 0.02 mmol), CuI (4 Mg, 0.02 mmol), Et_3N (0.22 mL, 1.6 mmol), and 2,6-di(*tert*-butyl)-4-methylphenol (1 mg) in CH_3CN (15 mL) was degassed *via* five freeze-pump-argon-thaw cycles, warmed to 23 °C, and stirred for 24 h. The mixture was diluted with ether, washed with aqueous $NaHCO_3$ and NaCl, dried over $MgSO_4$, filtered, and concentrated. The residue was analyzed by NMR spectrometry which indicated the formation of xerulin in 75% yield. Flash chromatography (silica gel, 30:70 EtOAc-hexane) afforded 75 mg of xerulin (70% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.84 (dd, J = 6.8, 1.9 Hz, 3 H), 5.61 (dqd, J = 15.6, 1.9, and 1.1 Hz, 1 H), 5.76 (d, J = 15.6 Hz, 1 H), 5.90 (d, J = 11.8 Hz, 1 H), 6.18 (d, J = 5.4 Hz, 1 H), 6.34 (dq, J = 15.8 and 7.0 Hz, 1 H), 6.4-6.55 (m, 3 H), 6.74-6.85 (m, 2 H), 7.37 (d, J = 5.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.99, 72.55, 79.40, 80.66, 83.36, 109.91, 112.15, 114.69, 118.89, 127.73, 135.07, 135.54, 137.81, 142.53, 143.79, 143.95, 149.46, 169.31; IR ($CDCl_3$) 3030, 2250, 2190, 1775, 1750, 1530, 1215, 1105, 1065, 995, 928, 895, 805, 765, 715

cm^{-1}. The ^1H and ^{13}C NMR spectral data are in good agreement with those reported in the literature.[d]

2-Propynoic Acid.[e] A mixture of 2-propynoic acid (1.4 g, 20 mmol) and NaI (4.8 g, 32 mmol) in acetic acid (10 mL) was heated at 70 °C for 24 h. Acetic acid was removed under vacuum, and subsequent purification by filtration over a short column of silica gel and concentration afforded 3.5 g of (*Z*)-3-iodoprop-2-enoic acid (89% yield) as a white solid: mp 66-67 °C (lit.[b] mp 63-65 °C); ^1H NMR ($CDCl_3$) δ 6.98 (d, J = 9.0 Hz, 1 H), 7.70 (d, J = 9.0 Hz, 1 H), 11.50 (brs, 1 H); ^{13}C NMR ($CDCl_3$) δ 98.19, 129.40, 170.04.

(a) For other method of preparation of (*E*)-1-iodo-2-bromoethylene, see: Viehe, H. G.; Franchimont, E. *Chem. Ber.* **1963**, *96*, 3153.

(b) Acetylene was purified by passing through water, H_2SO_4, KOH pellets and remove cold trap (-78 °C).

(c) Purchased from Aldrich.

(d) Kuhnt, D.; Anke, T.; Besl, H.; Bross, M.; Herrmann, R.; Mocek, U.; Steffan, B.; Steglich, W. *J. Antibiotics* **1990**, *43*, 1413.

(e) Stolz, R. *Chem. Ber.* **1886**, *19*, 536.

I ⊥ Br

A633CH1
SPECTRAL LINES FOR TH= 0.50
RFL= 420.7 RFP= 0

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02	1380.70	6.904	29.052
03	1367.27	6.837	101.217
04	1357.79	6.790	100.936
05	1344.35	6.723	29.518
06	310.23	1.551	23.601

A633CH1
200MHZ

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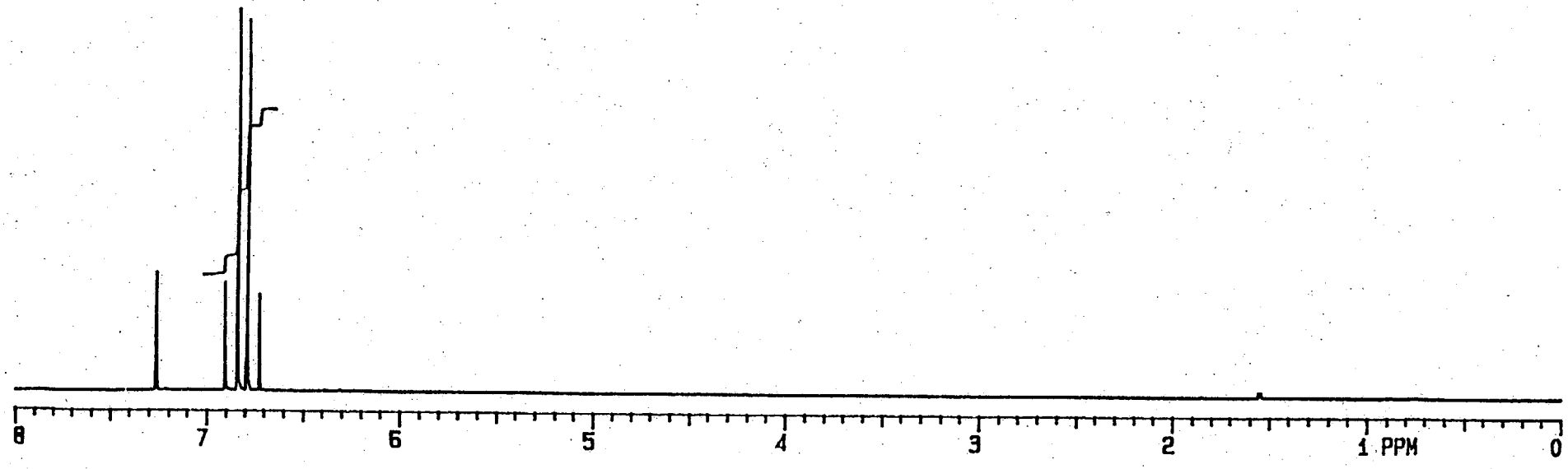
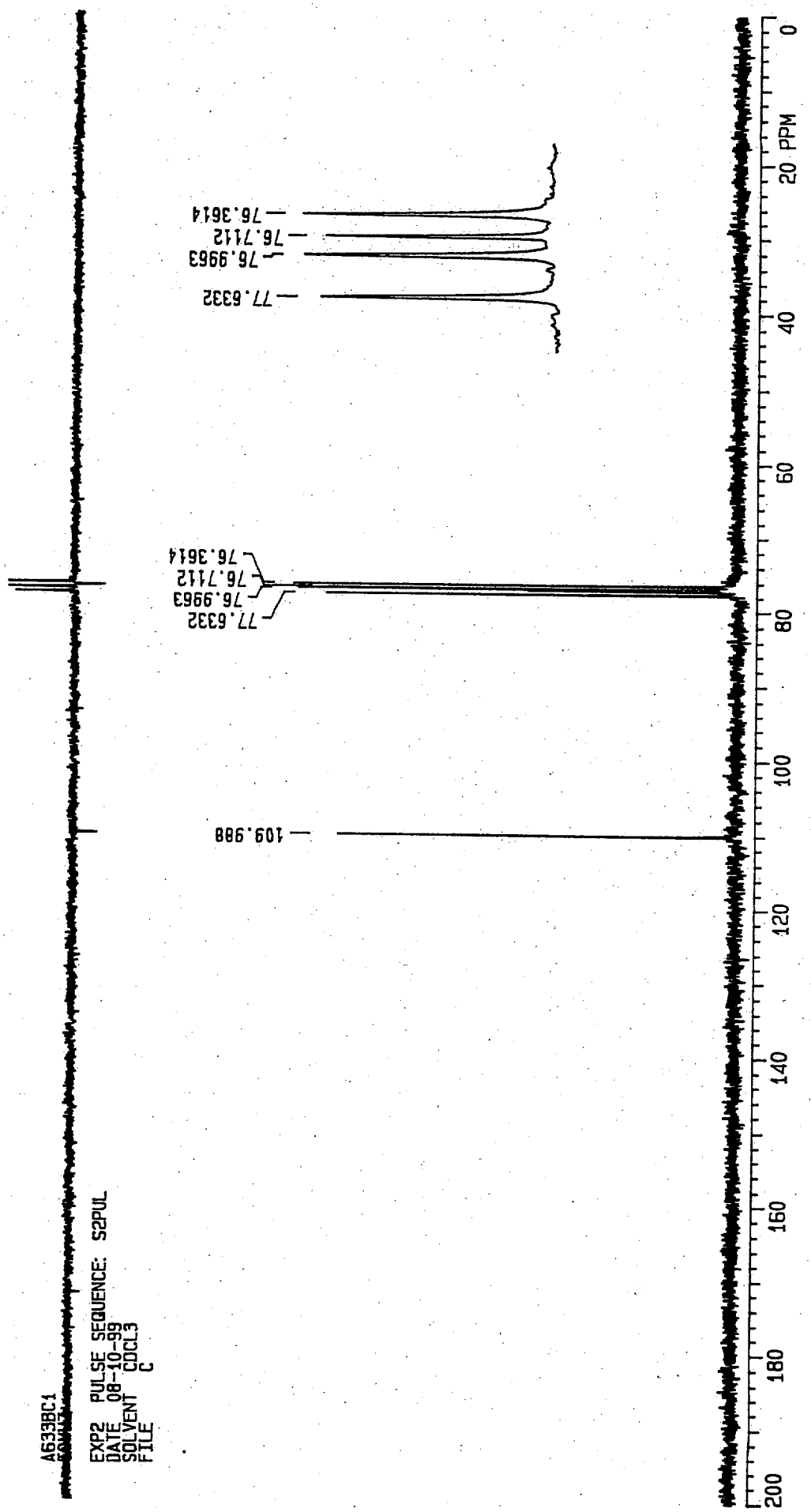
DATE 08-18-99
SOLVENT CDCL3
FILE H





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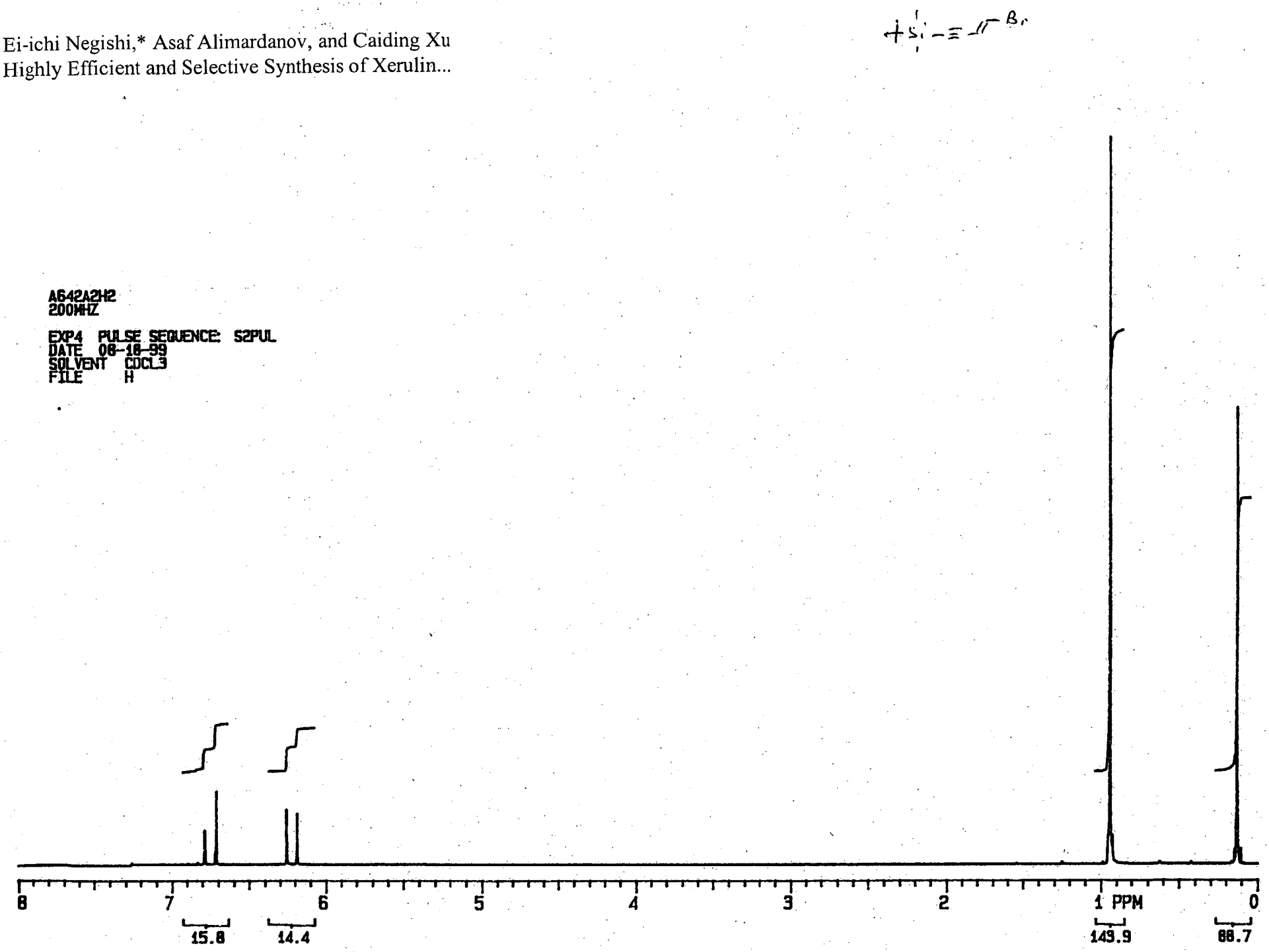

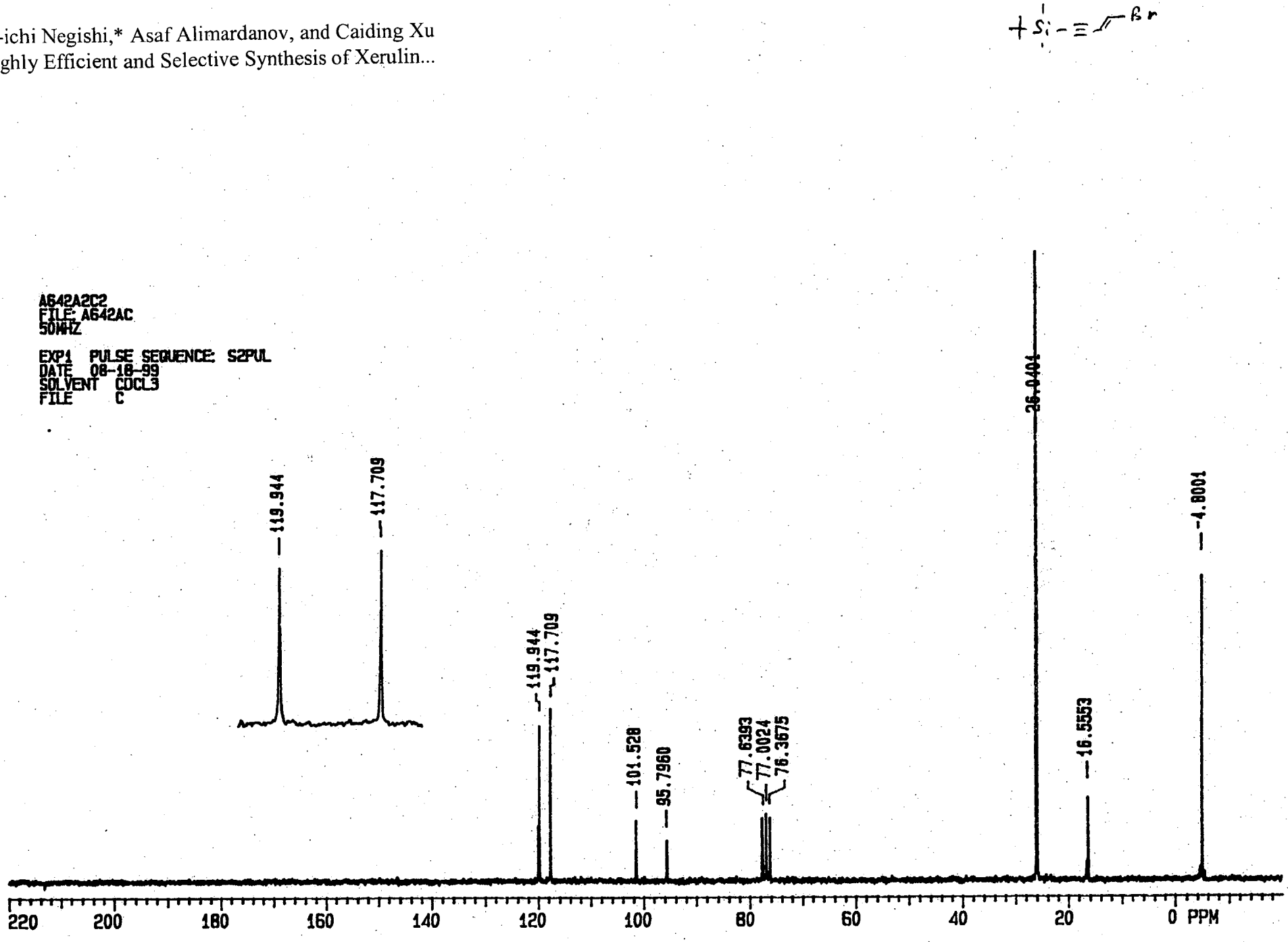

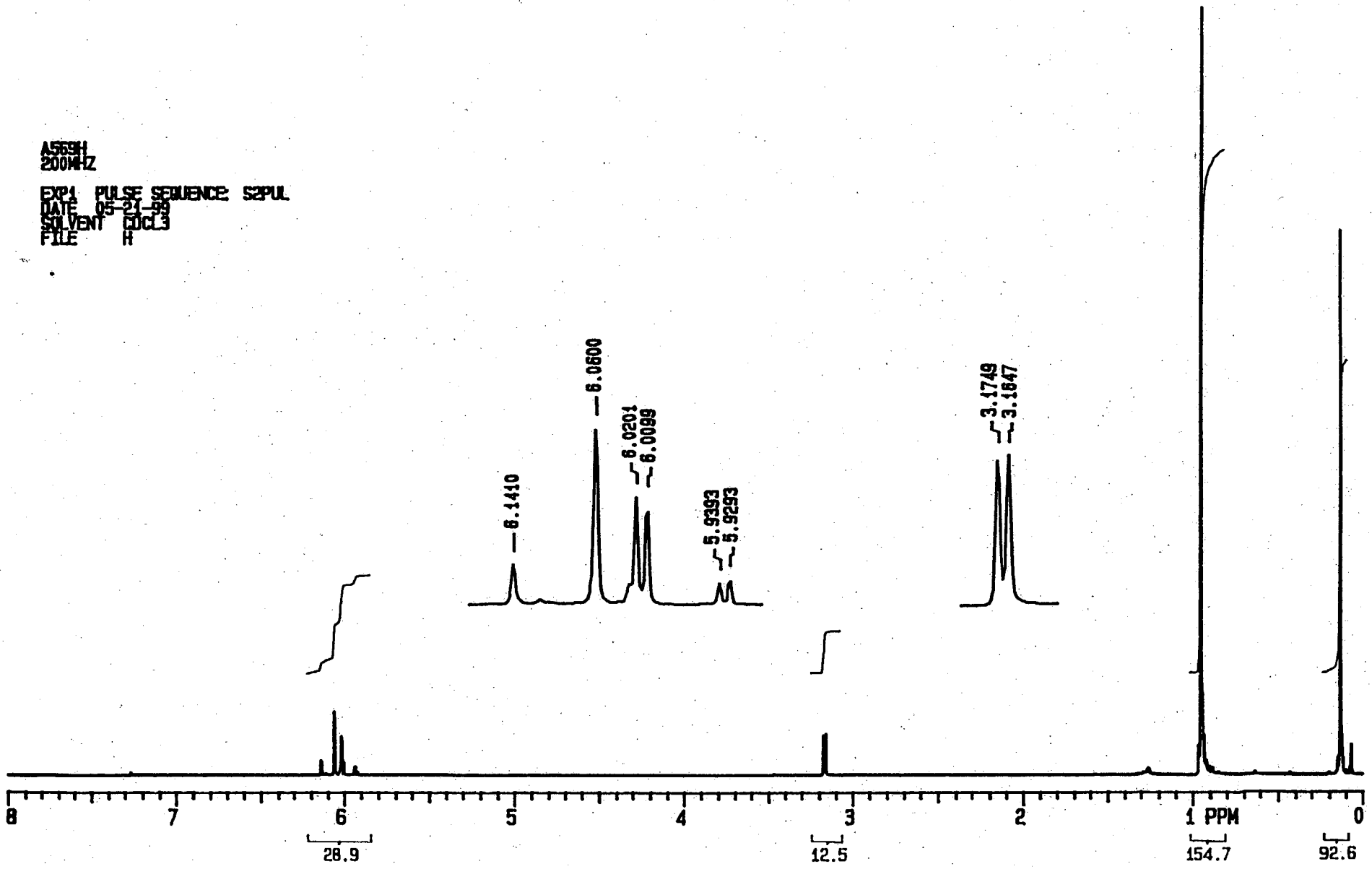

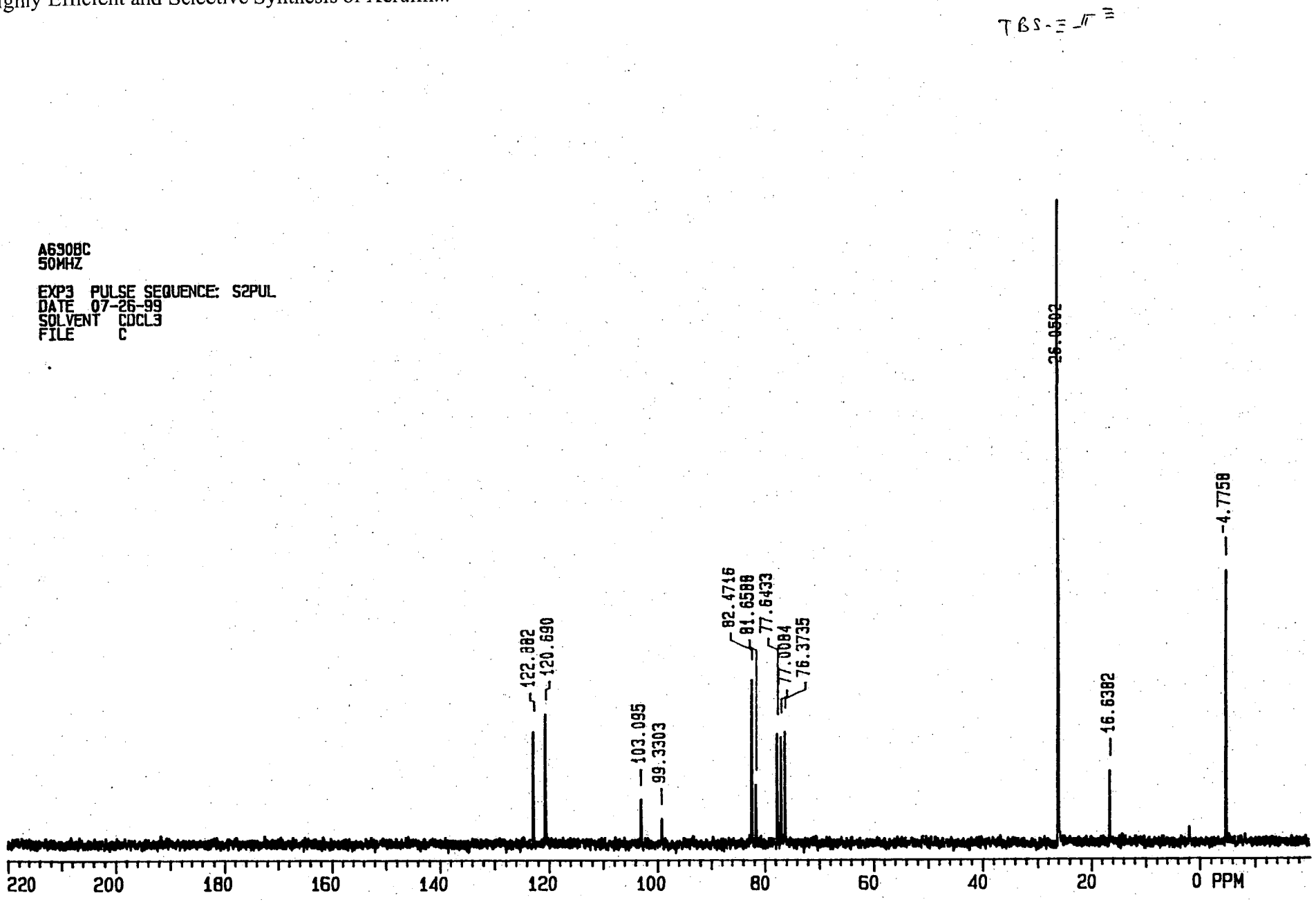

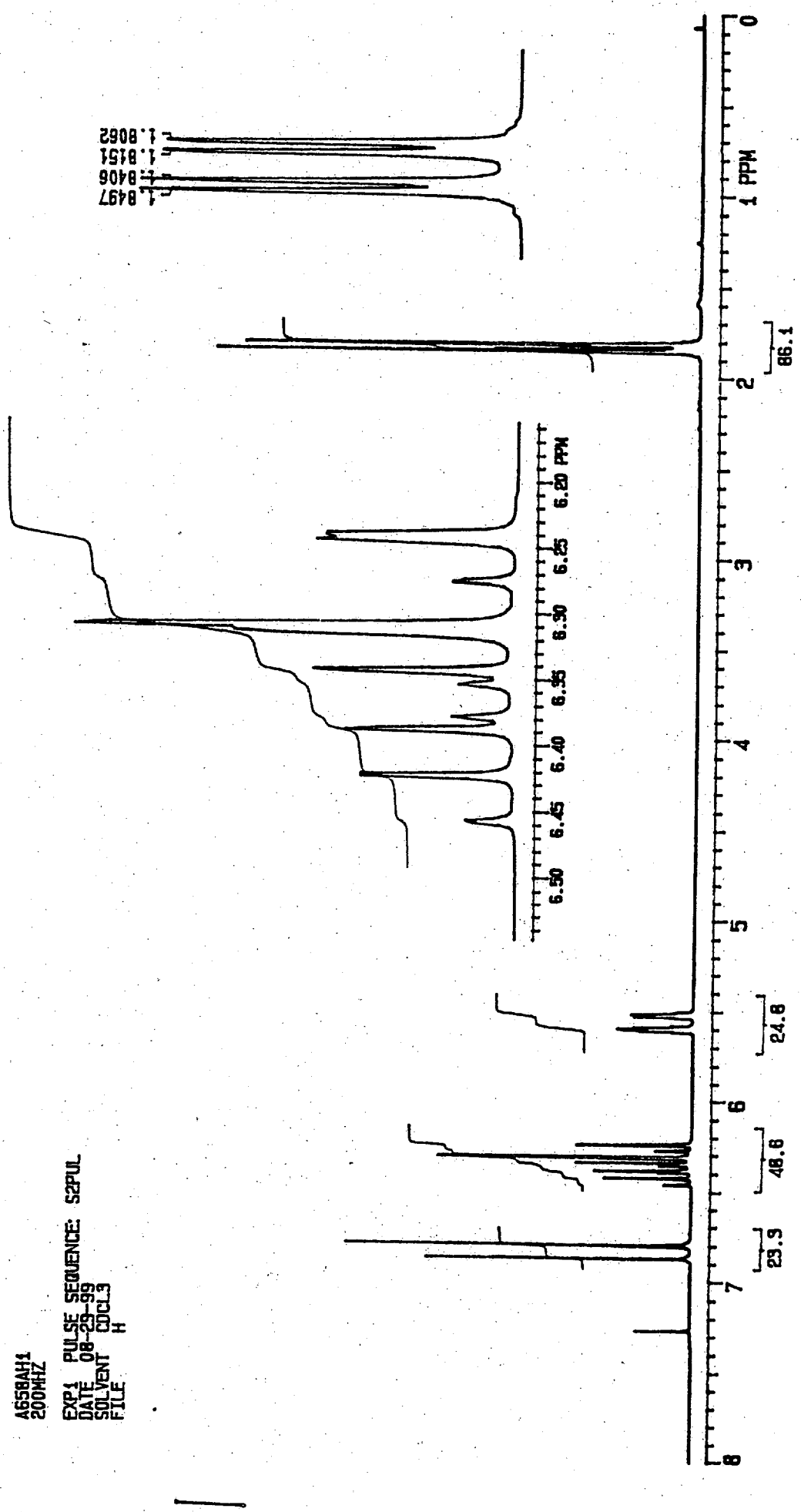

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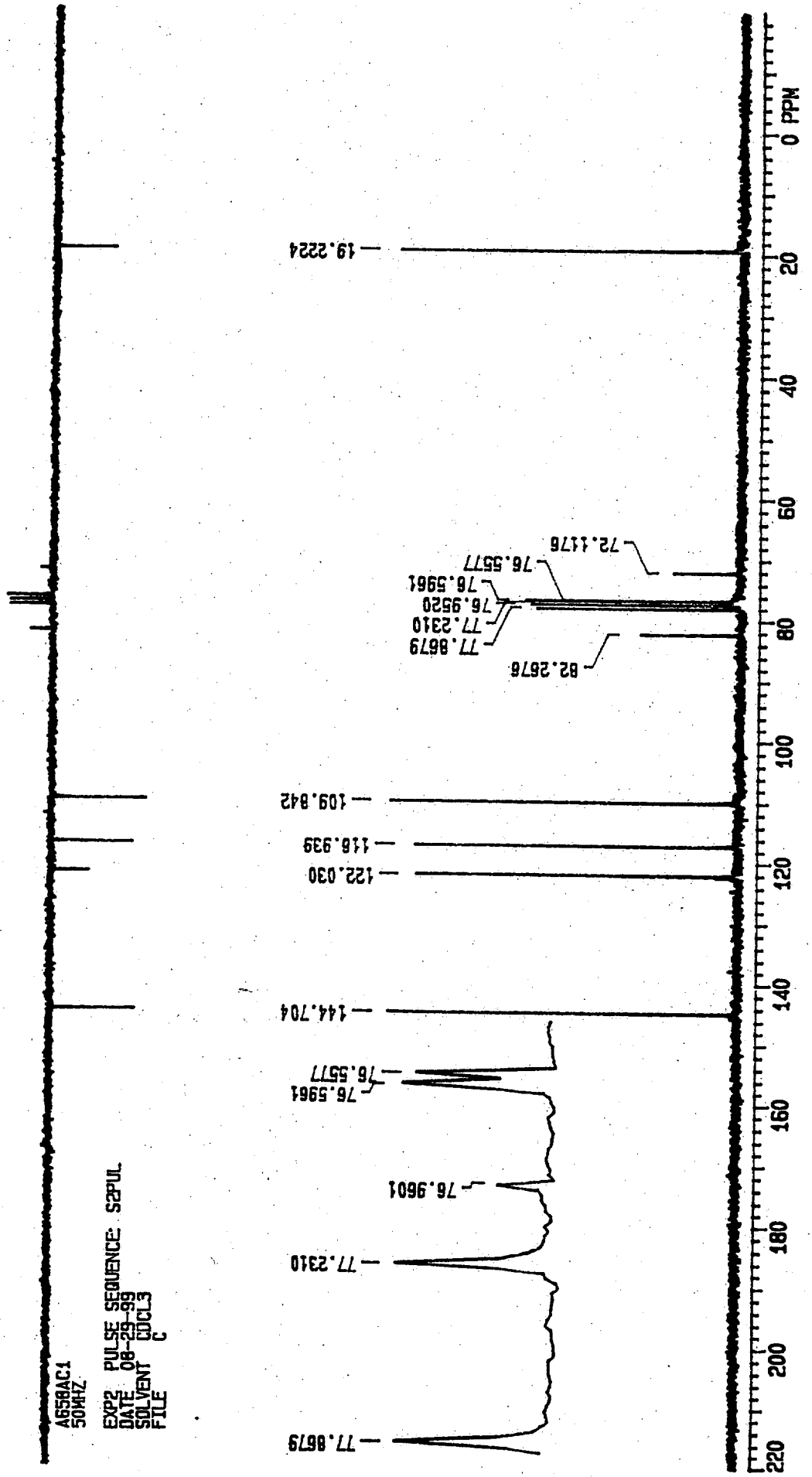

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a674h3
500mhz
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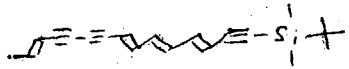

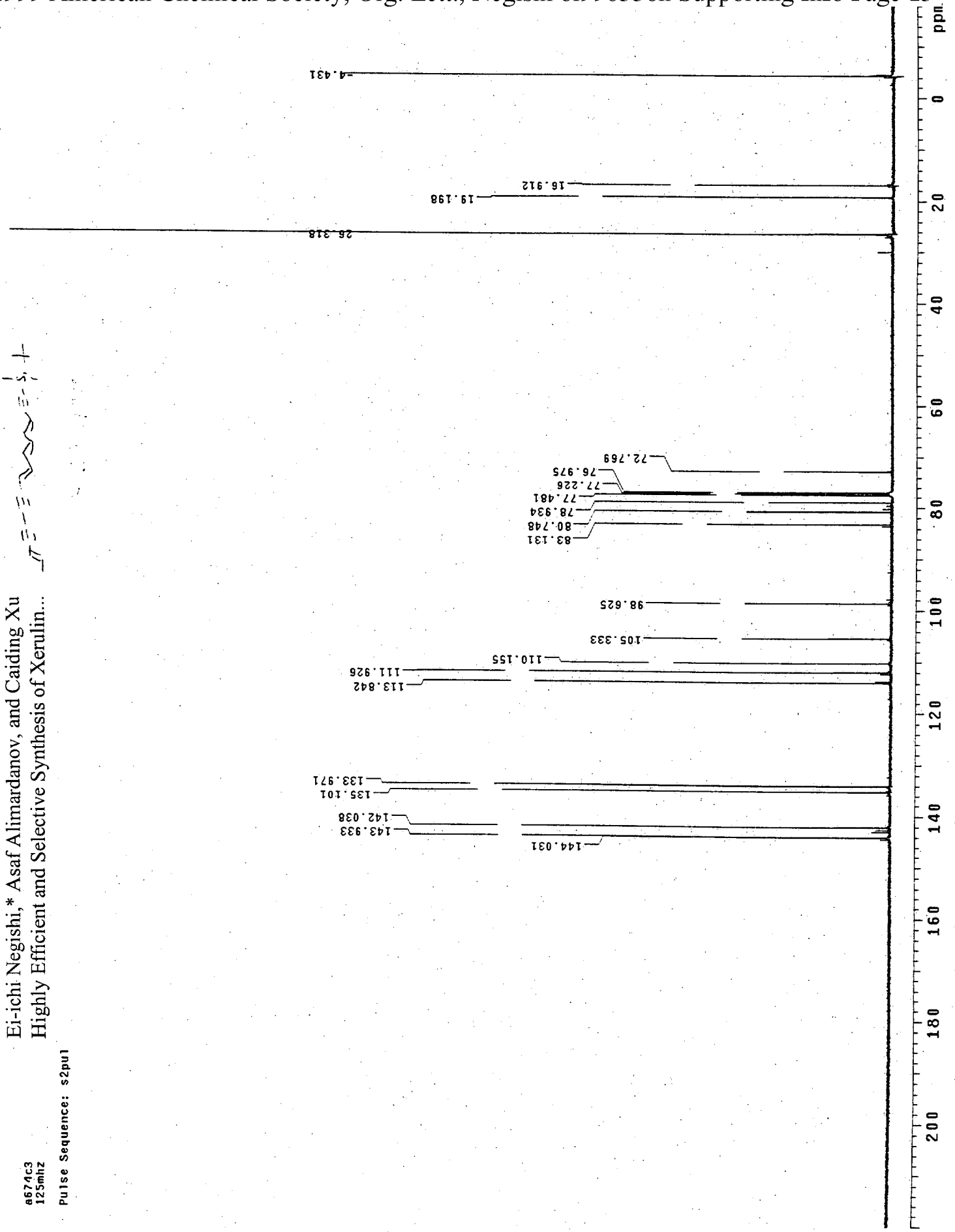

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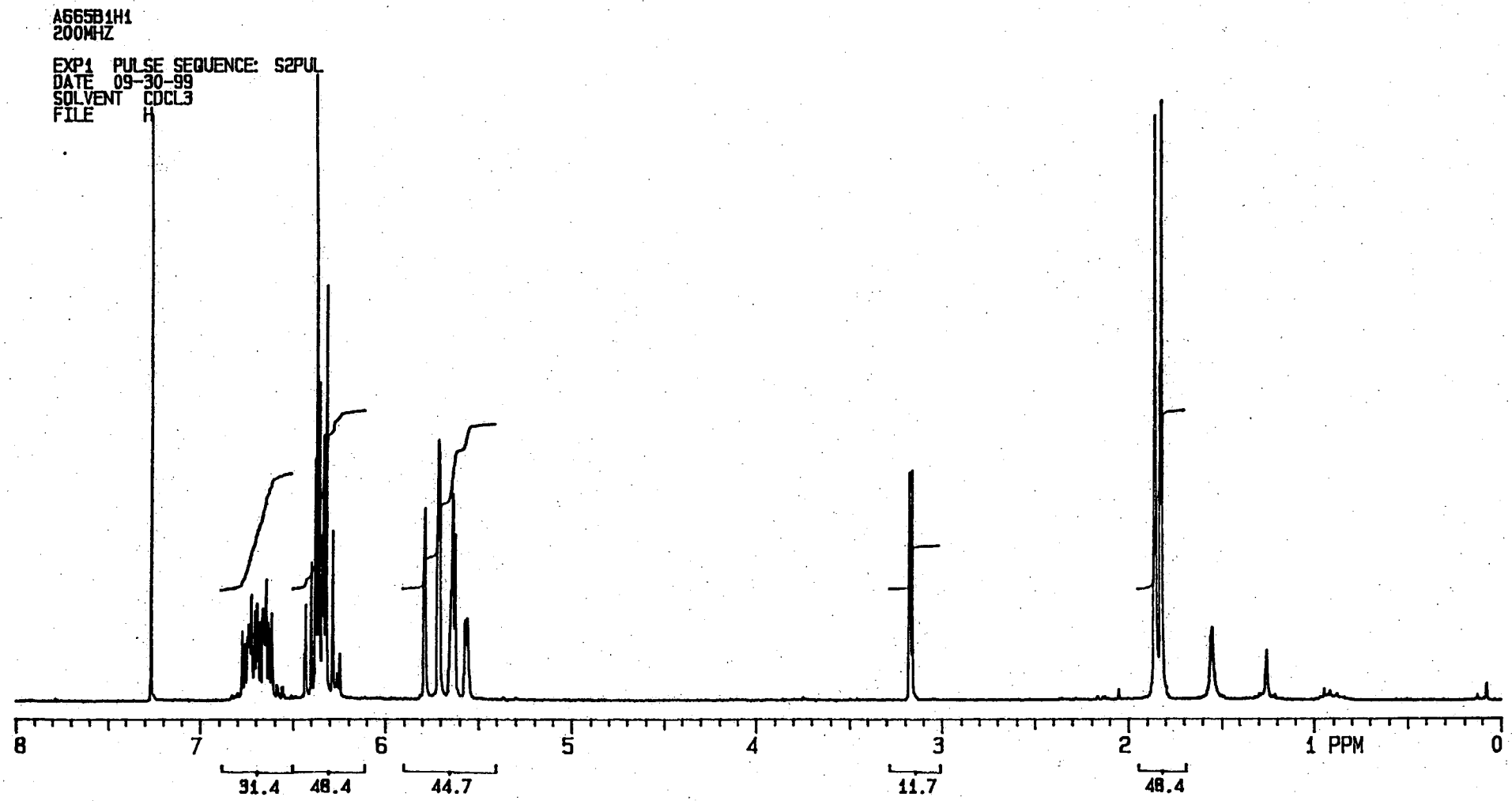

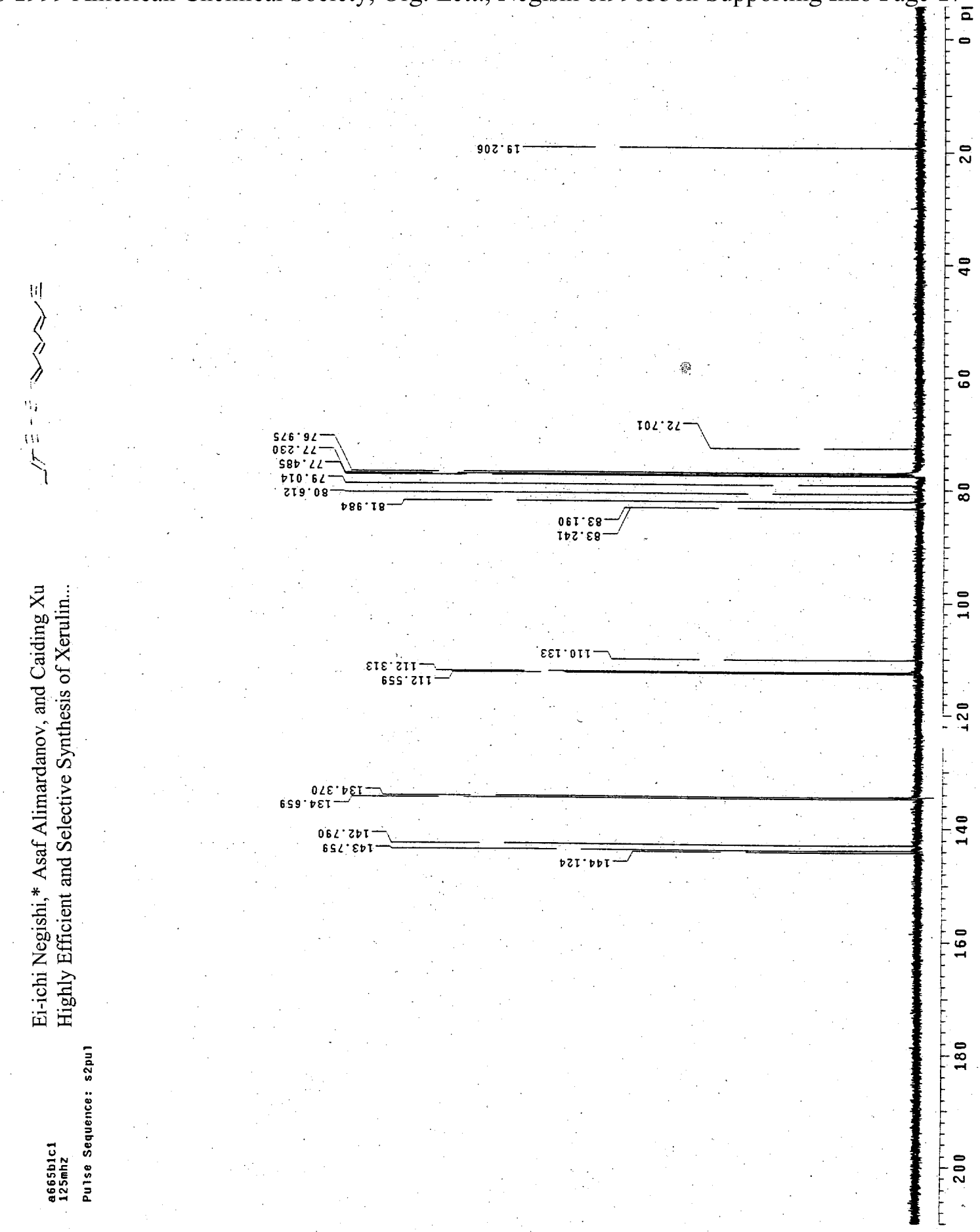

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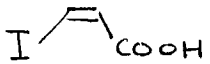
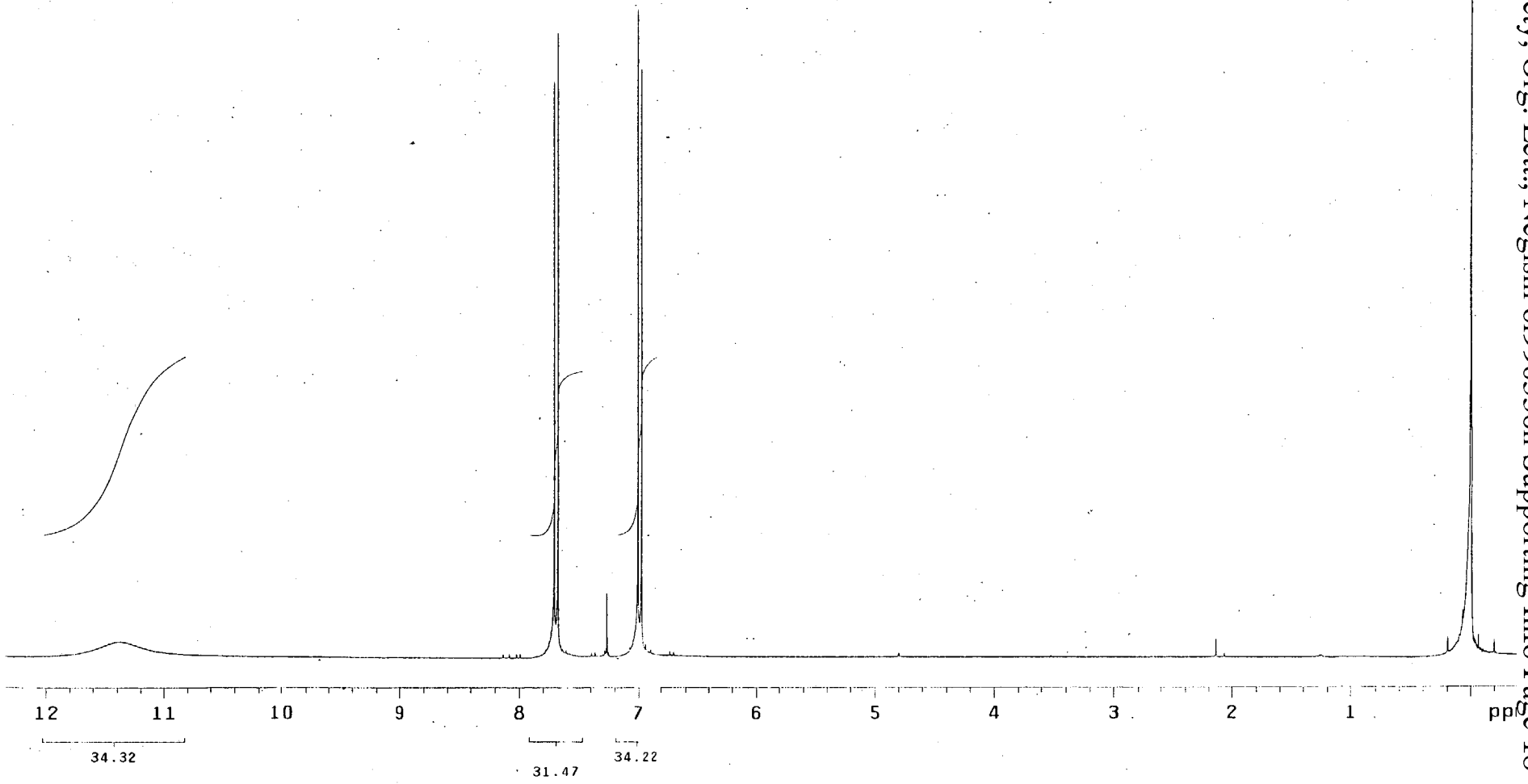
1	2312.998	7.711	94.2
2	2303.995	7.681	102.0
3	2102.573	7.010	105.8
4	2093.570	6.979	96.2
5	-0.000	-0.000	564.6
6	-0.305	-0.001	514.7





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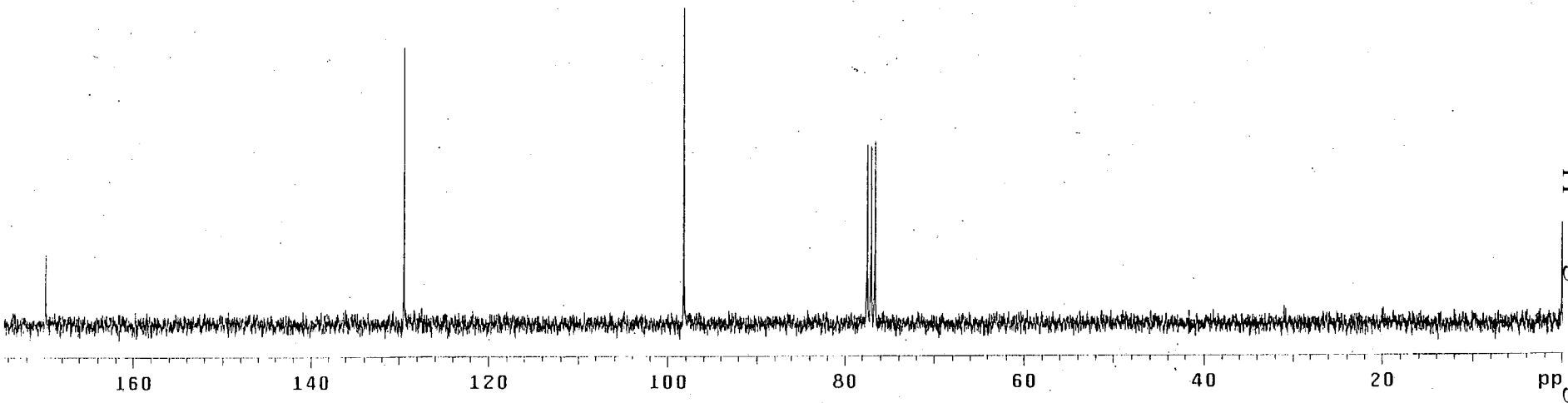
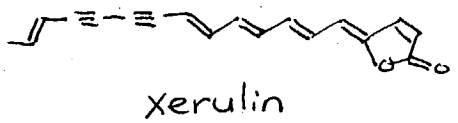
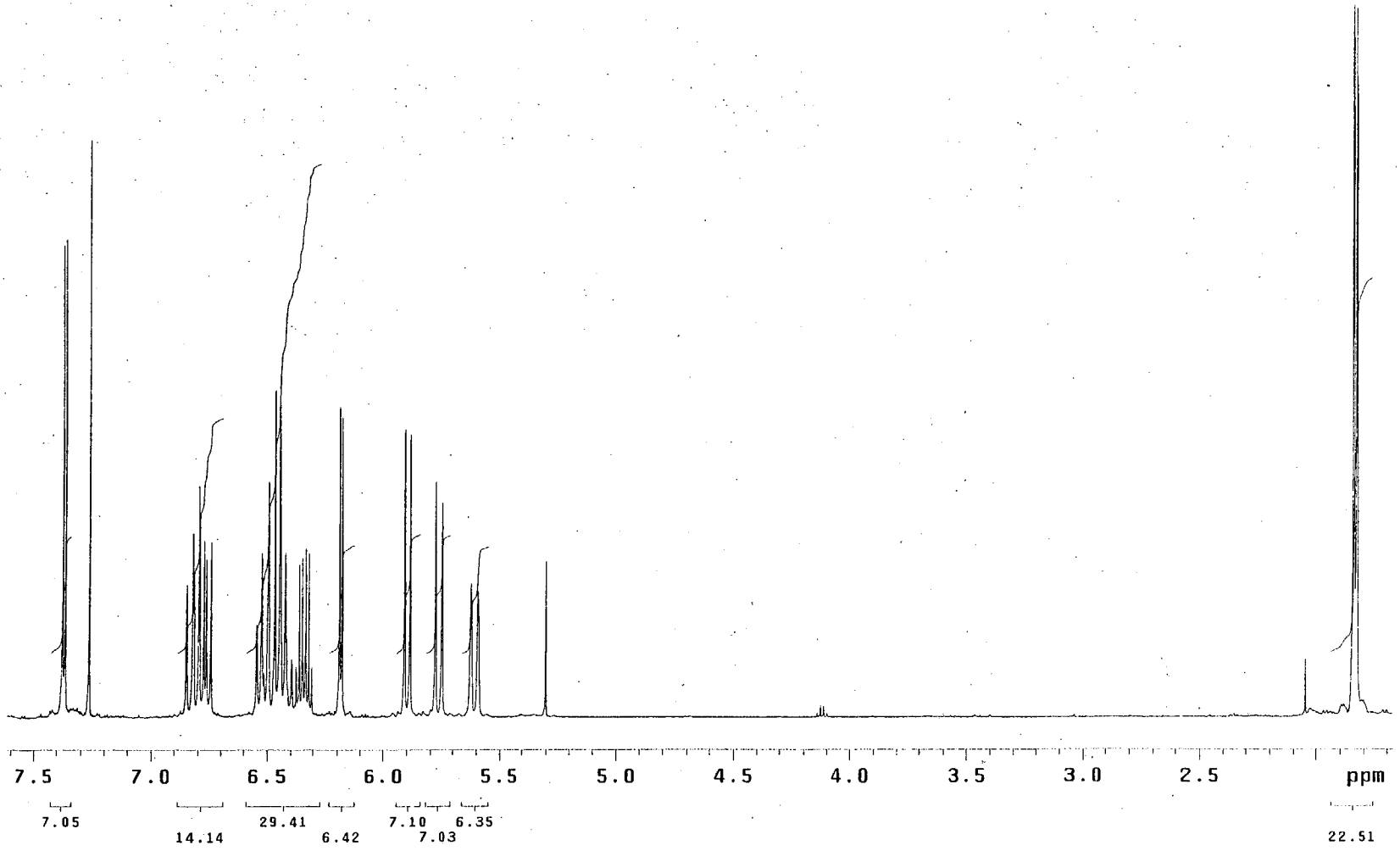
1	9760.525	129.407	43.8
2	7405.664	98.186	50.0
3	5838.443	77.407	28.4
4	5806.716	76.987	28.2
5	5774.485	76.559	29.0





Xerulin



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1	3686.287	7.375	74.0	40	915.695	1.832	110.6
2	3680.916	7.364	74.9	41	913.985	1.829	100.0
3	3629.889	7.262	90.3				
4	3421.142	6.844	20.6				
5	3409.423	6.821	28.6				
6	3406.981	6.816	22.3				
7	3396.483	6.795	36.2				
8	3395.507	6.793	31.4				
9	3385.985	6.774	27.5				
10	3381.102	6.764	24.6				
11	3370.603	6.743	27.3				
12	3270.747	6.544	14.4				
13	3260.248	6.523	25.5				
14	3245.355	6.493	36.9				
15	3231.683	6.465	51.3				
16	3222.161	6.446	50.0				
17	3211.175	6.424	25.7				
18	3208.733	6.419	12.2				
19	3180.656	6.363	23.8				
20	3173.576	6.349	24.9				
21	3166.740	6.335	10.5				
22	3164.787	6.332	26.3				
23	3157.950	6.318	25.5				
24	3093.495	6.189	48.7				
25	3088.124	6.178	47.0				
26	2953.110	5.908	45.1				
27	2941.391	5.885	44.3				
28	2886.946	5.776	36.8				
29	2871.565	5.745	33.5				
30	2812.237	5.626	20.1				
31	2811.016	5.624	20.9				
32	2809.307	5.620	16.8				
33	2796.367	5.594	18.7				
34	2795.391	5.593	19.7				
35	2794.658	5.591	18.4				
36	2793.682	5.589	15.7				
37	2649.146	5.300	24.2				
38	922.531	1.846	111.0				
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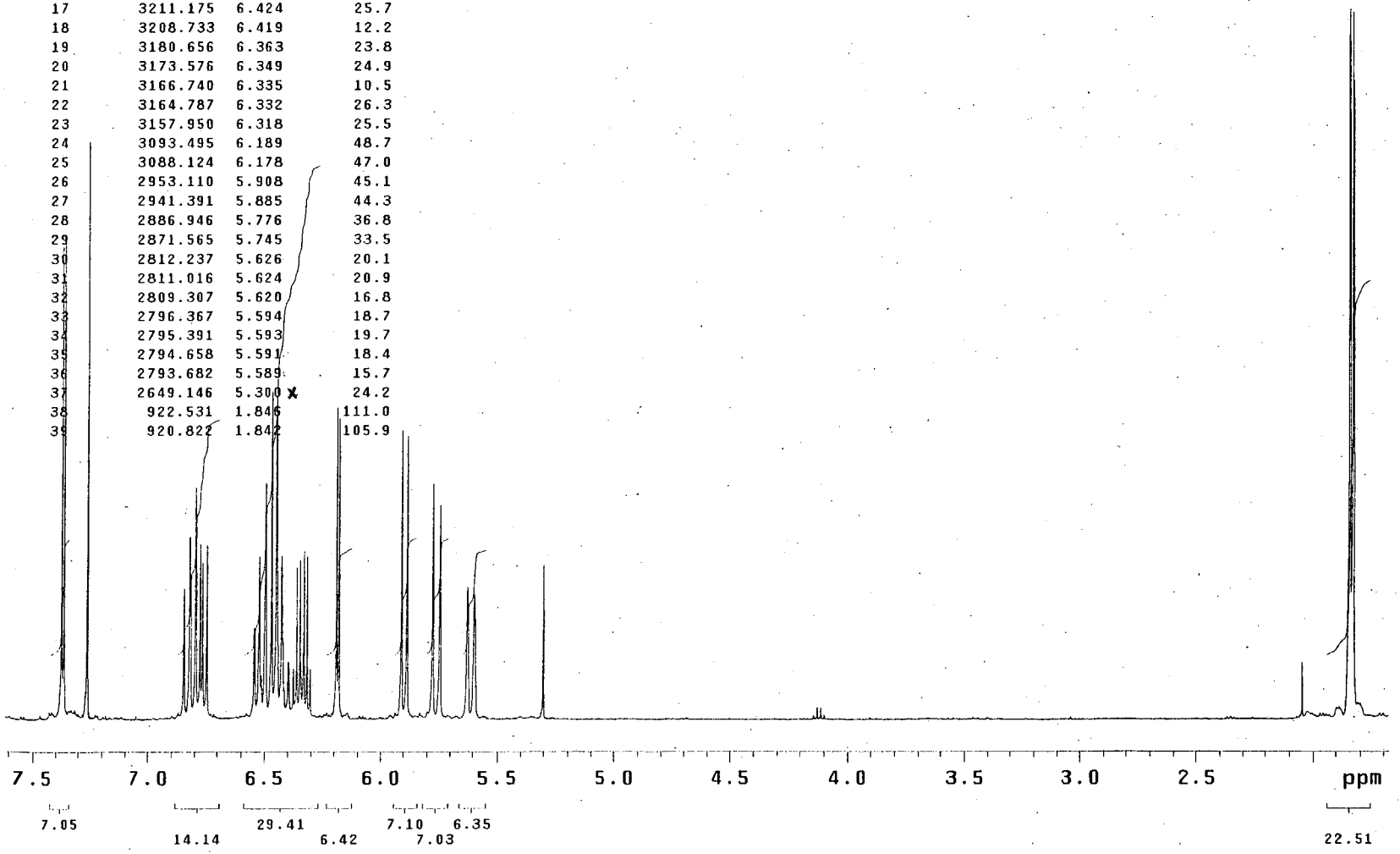

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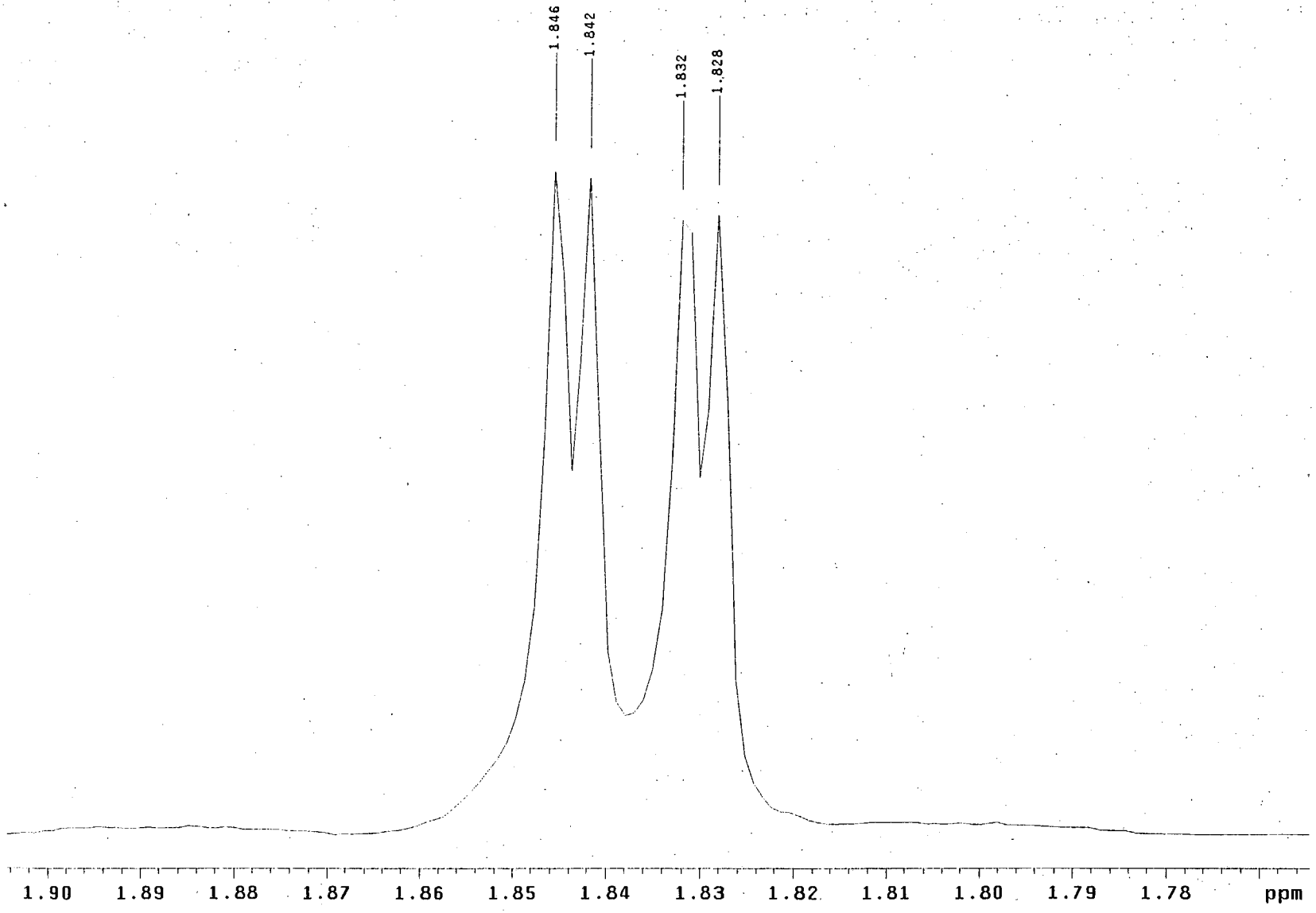

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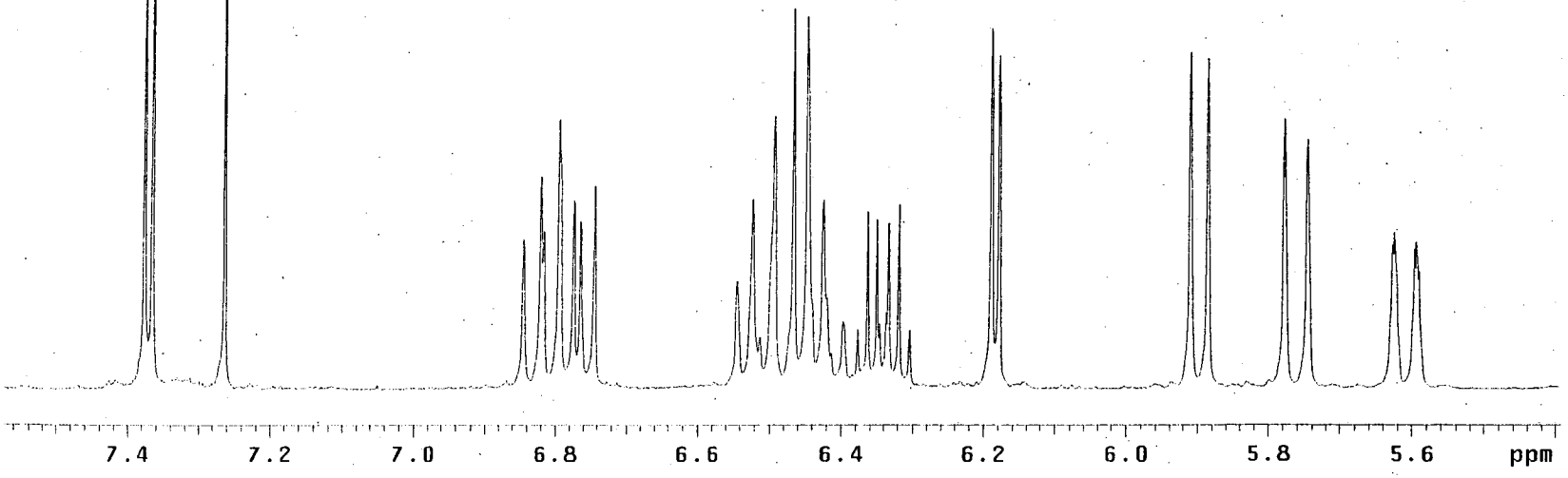
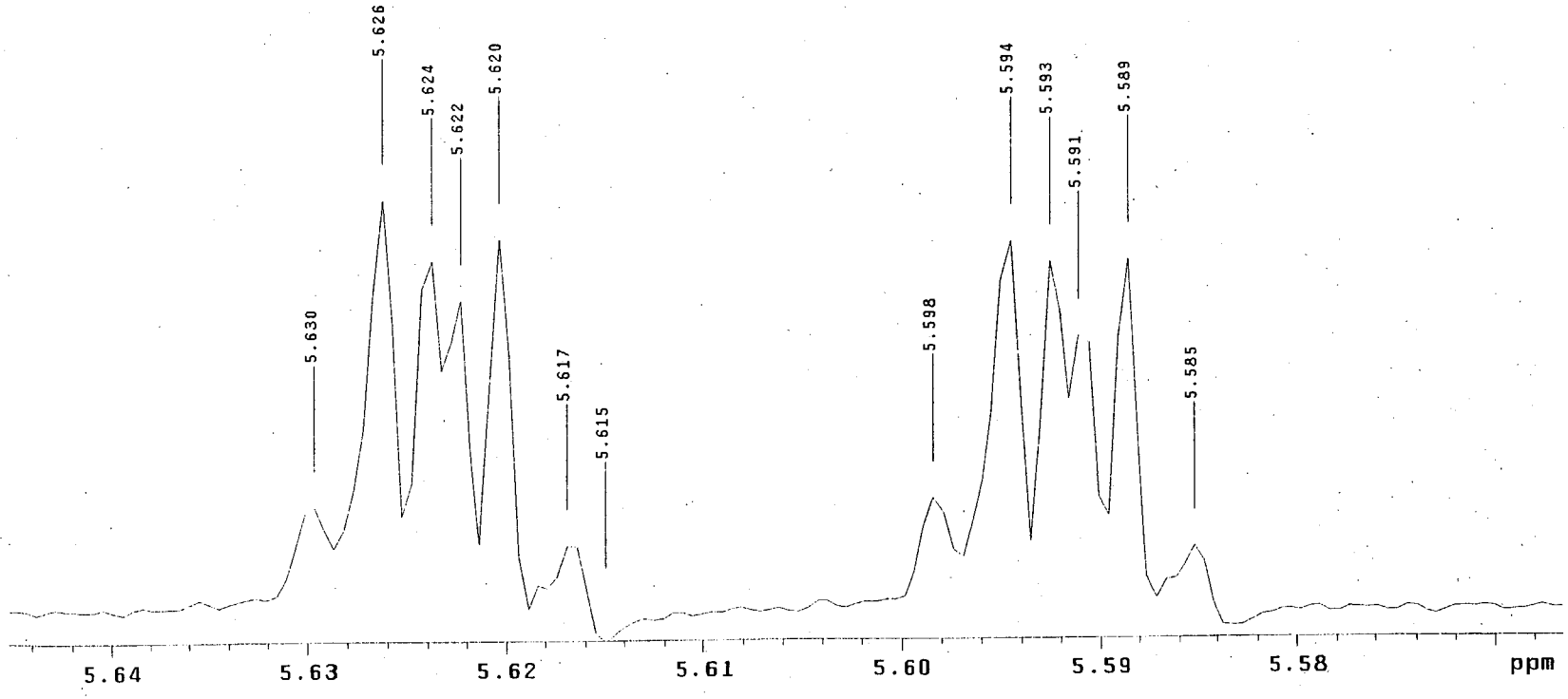
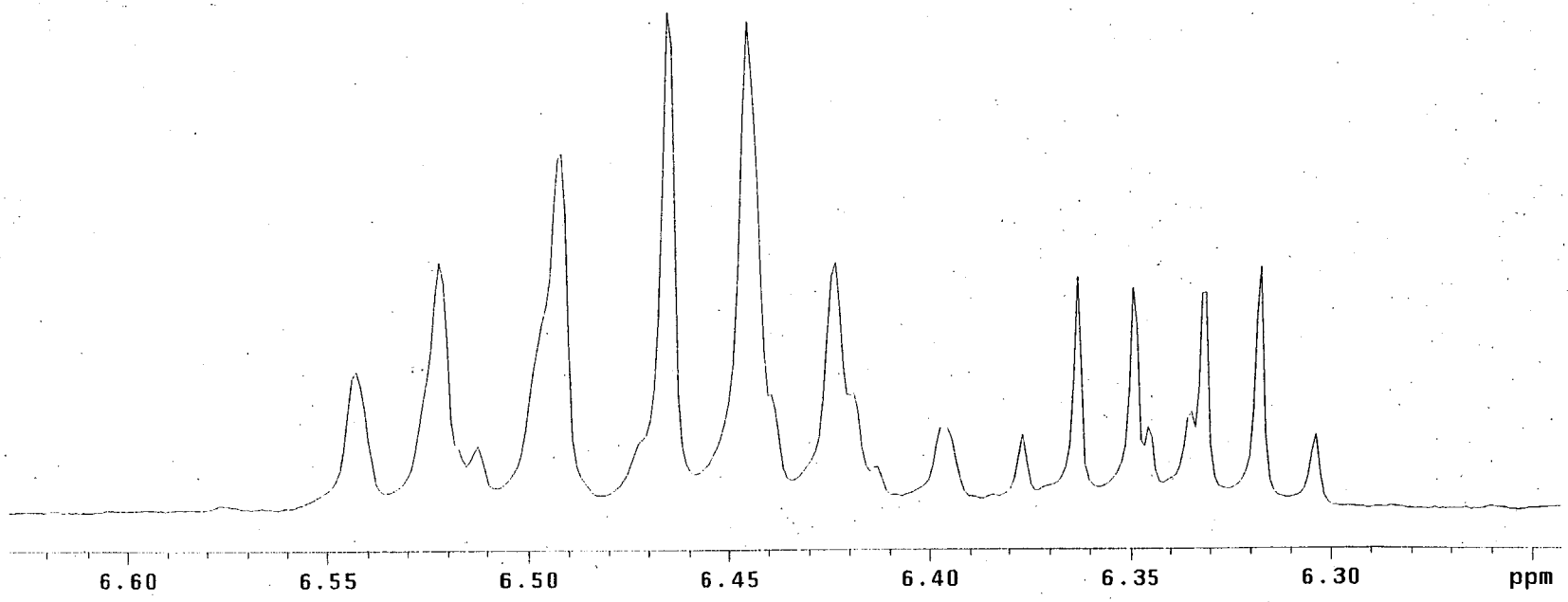
4	3421.292	6.845	20.7
5	3409.085	6.820	29.6
6	3407.131	6.816	21.9
7	3396.389	6.795	37.5
8	3386.134	6.774	26.3
9	3381.251	6.765	23.3
10	3370.508	6.743	28.3
11	3270.404	6.543	15.0
12	3260.150	6.522	26.5
13	3255.267	6.513	7.2
14	3245.012	6.492	38.0
15	3231.828	6.466	53.0
16	3222.061	6.446	51.9
17	3210.830	6.424	26.3
18	3205.459	6.413	4.9
19	3197.158	6.396	9.2
20	3187.391	6.377	8.2
21	3180.555	6.363	24.7
22	3173.719	6.349	23.6
23	3171.765	6.345	9.0
24	3166.394	6.335	10.5
25	3164.441	6.331	23.1
26	3157.604	6.317	25.7
27	3150.768	6.303	8.1
28	3093.147	6.188	50.2
29	3087.776	6.177	46.4
30	2953.002	5.908	46.8
31	2941.283	5.884	46.0
32	2887.080	5.776	37.6
33	2871.454	5.745	34.8
34	2811.880	5.625	20.1
35	2810.904	5.624	21.7
36	2796.254	5.594	19.4
37	2795.278	5.592	20.4
38	2793.324	5.588	16.3



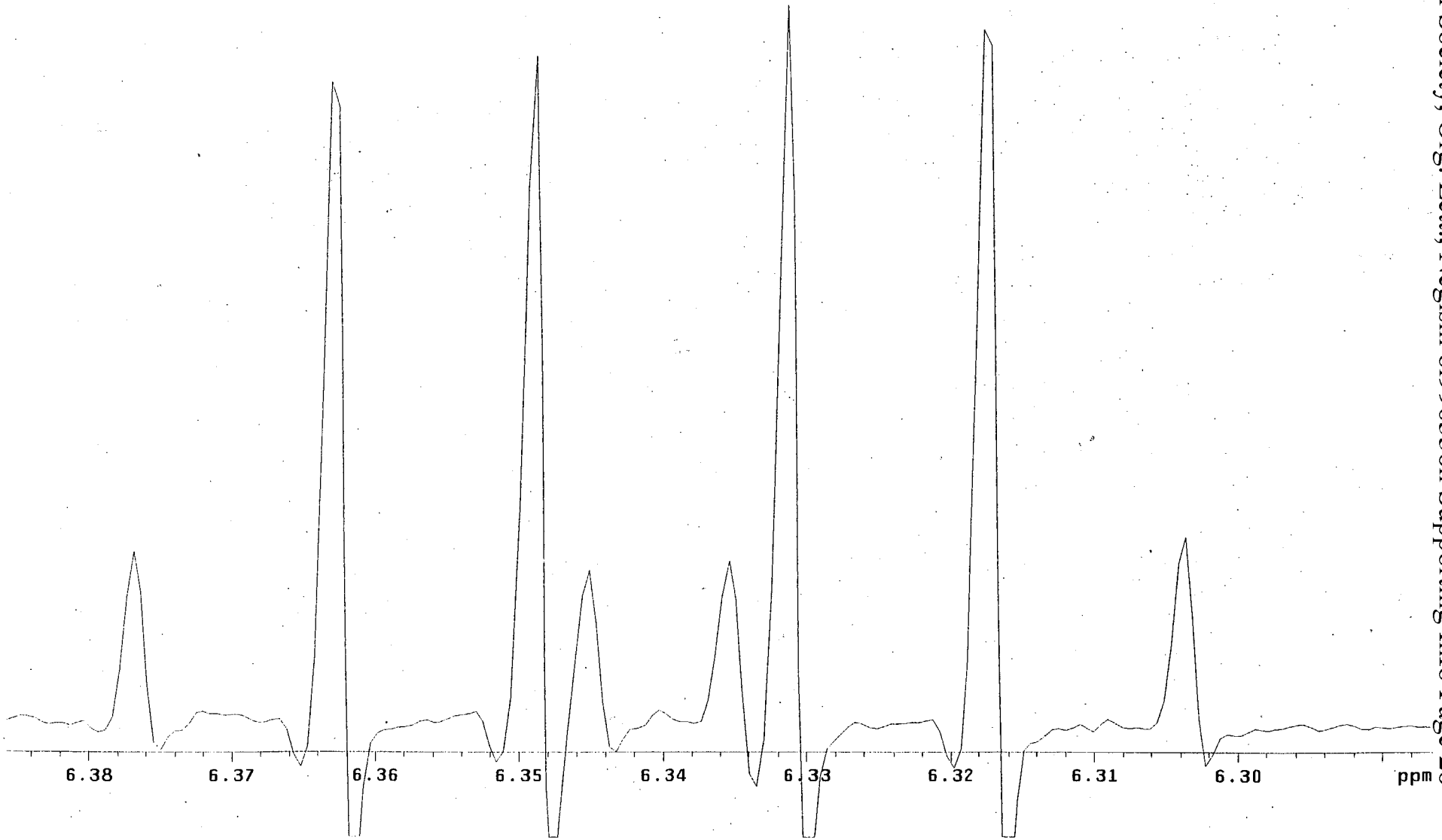
INDEX	FREQUENCY	PPM	HEIGHT
1	2813.946	5.630	13.8
2	2812.237	5.626	56.5
3	2811.016	5.624	48.0
4	2810.284	5.622	42.5
5	2809.307	5.620	50.9
6	2807.598	5.617	8.2
7	2806.621	5.615	-5.2
8	2798.320	5.598	14.6
9	2796.367	5.594	50.3
10	2795.391	5.593	47.4
11	2794.658	5.591	37.1
12	2793.437	5.589	47.6
13	2791.728	5.585	7.7



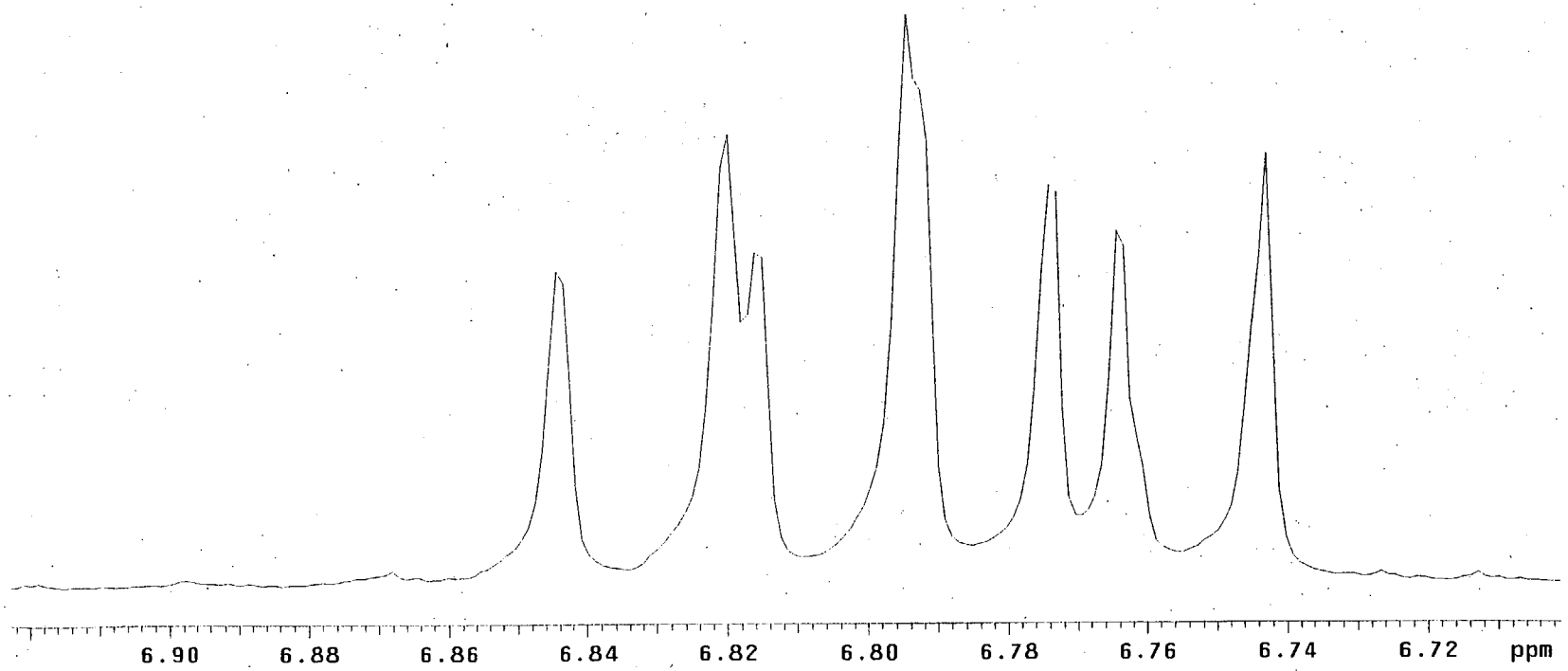
INDEX	FREQUENCY	PPM	HEIGHT
1	3270.404	6.543	19.8
2	3260.150	6.522	35.0
3	3255.267	6.513	9.5
4	3245.012	6.492	50.3
5	3231.828	6.466	70.1
6	3222.061	6.446	68.7
7	3210.830	6.424	34.8
8	3205.459	6.413	6.5
9	3197.158	6.396	12.2
10	3187.391	6.377	10.9
11	3180.555	6.363	32.7
12	3173.719	6.349	31.2
13	3171.765	6.345	11.9
14	3166.394	6.335	13.9
15	3164.441	6.331	30.5
16	3157.604	6.317	34.0
17	3150.768	6.303	10.8

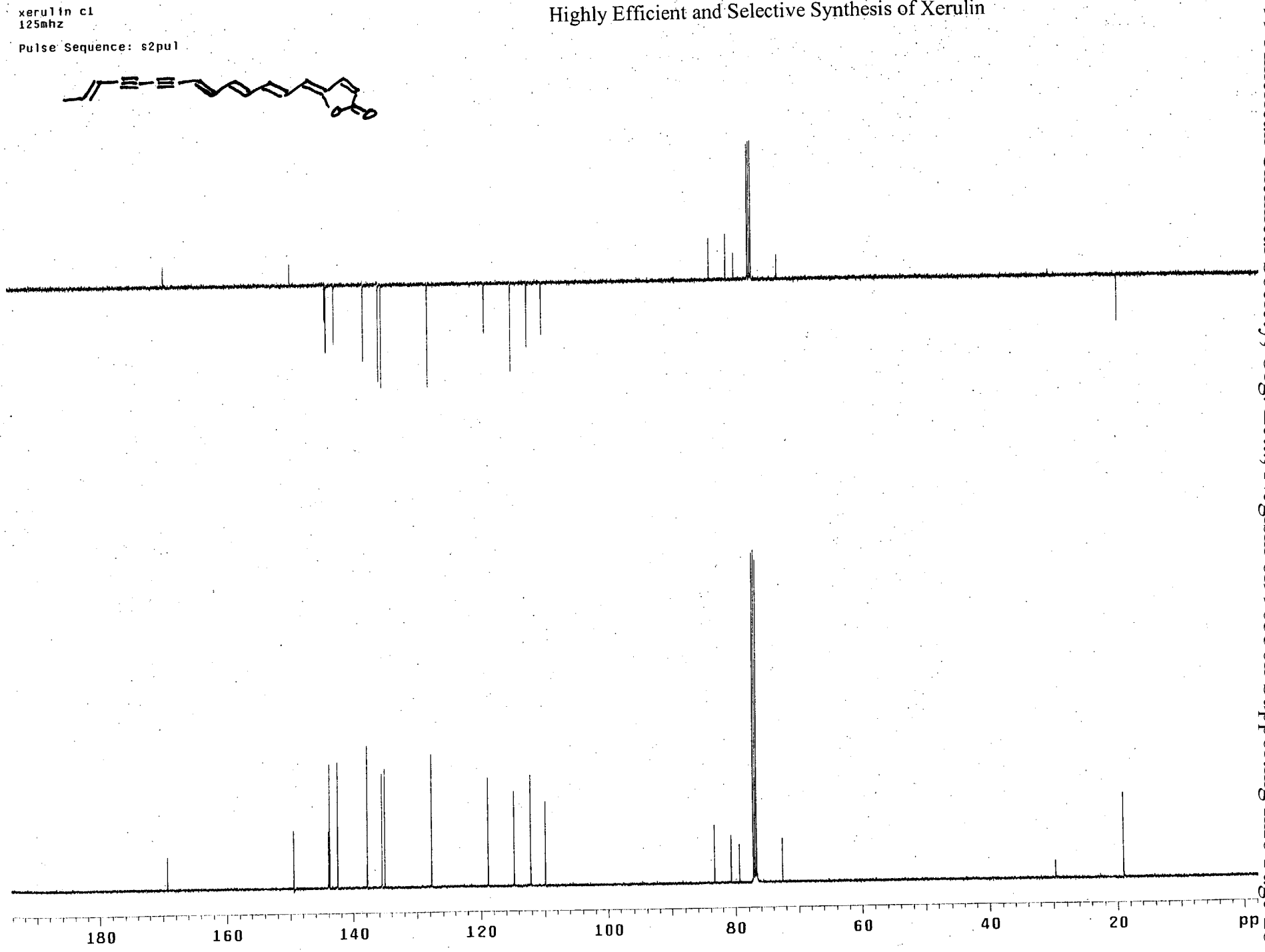


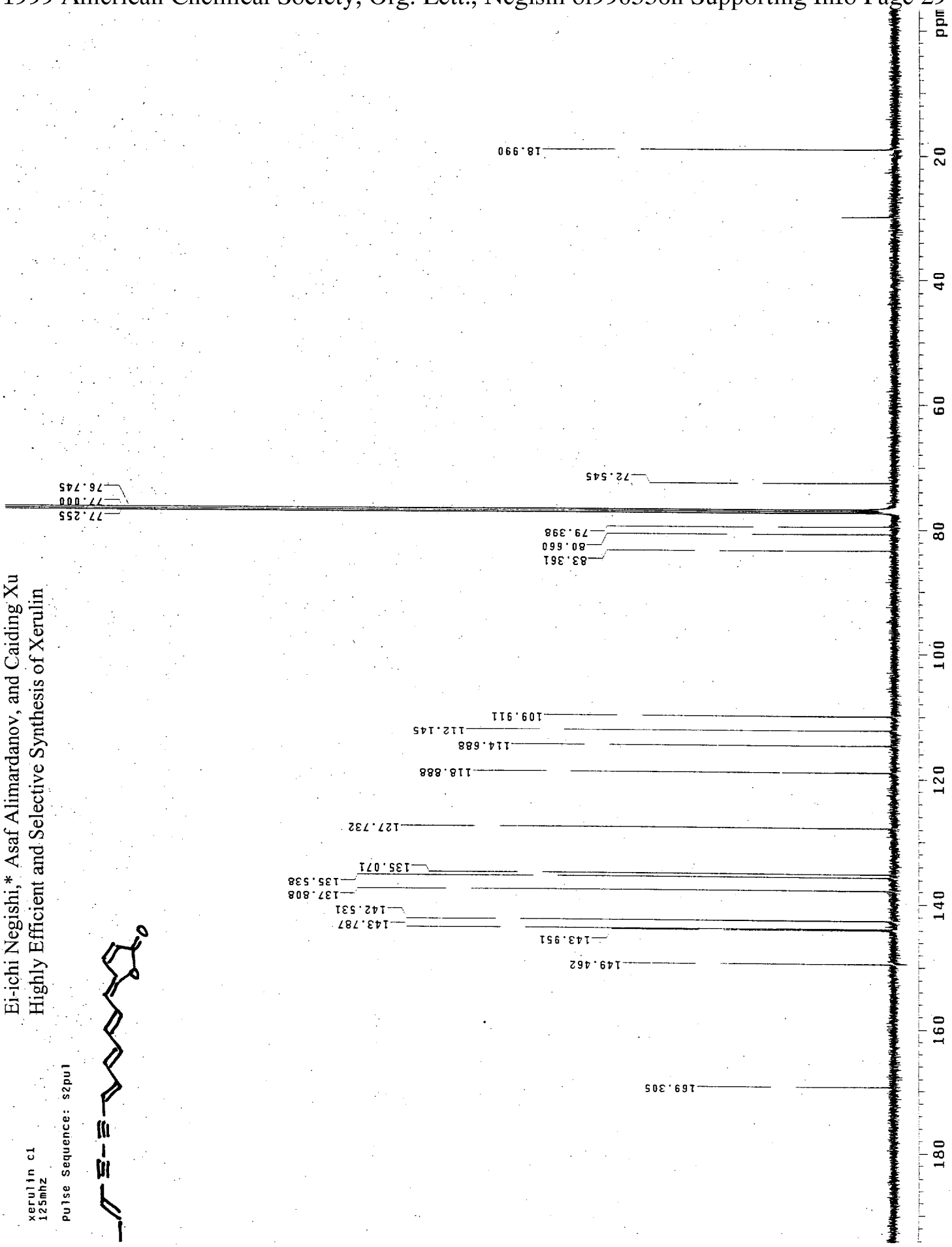
INDEX	FREQUENCY	PPM	HEIGHT
1	3187.492	6.377	30.2
2	3180.656	6.363	112.8
3	3179.680	6.361	-27.7
4	3173.576	6.349	117.4
5	3172.843	6.348	-31.1
6	3171.623	6.345	26.8
7	3166.740	6.335	28.6
8	3164.787	6.332	126.5
9	3164.054	6.330	-32.5
10	3157.950	6.318	122.2
11	3156.974	6.316	-31.1
12	3150.870	6.304	32.7



INDEX	FREQUENCY	PPM	HEIGHT
1	3421.292	6.845	44.3
2	3409.085	6.820	63.4
3	3407.131	6.816	46.9
4	3396.389	6.795	80.3
5	3386.134	6.774	56.2
6	3381.251	6.765	49.7
7	3370.508	6.743	60.5







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Highly Efficient and Selective Synthesis of Xerulin